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16. Abstract (Limit: 200 words)

One hundred individuals who had experienced organophosphate pesticide poisonings were matched with 100 individuals who had never been poisoned but were similar in age, sex, race, ethnic background, education and occupational class but not occupation. None of the control subjects had any occupational exposure to pesticides while 96% of the poisoned individuals worked with pesticides professionally. Both groups underwent extensive testing for neurological and psychological function. No statistically significant differences in neurological function were detected between the poisoned group and controls. Statistically significant differences were found in certain psychological tests. Both groups tested above average in intelligence, but the control group scored 5 points higher on the average on adult IQ tests. For the most part, the control group scored higher in areas related to academic skills. In self-assessments of psychological function, the control group scored higher in the same areas. Several important sources of bias in the study design may have effected the results. The effects observed were subtle. None of the poisoned individuals had ever sought medical care for chronic effects or claimed any noticeable decrease in their intellectual or psychological function as a result of their poisoning.

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CHRONIC NEUROLOGICAL SEQUELAE OF ACUTE ORGANOPHOSPHATE PESTICIDE POISONING: AN EPIDEMIOLOGIC STUDY

Final Report

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INTRODUCTION

The increased use of organophosphate (OP) pesticides in the last three decades has been accompanied by numerous acute organophosphate poisonings. The World Health Organization (WHO) has stated that the problem of acute pesticide poisonings is extensive and serious and may number as many as 500,000 cases annually throughout the world (1). In the United States, a national study of hospitalized pesticide poisoning cases from 1971 through 1973 resulted in an estimated 8241 admissions of which 31% were due to organophosphate pesticides. Of these, over 70% of the organophosphate pesticide poisonings were due to occupational exposure (2).

The OP pesticides are cholinesterase inhibitors. In the poisoned individual cholinergic synapses cannot degrade the transmitter, acetylcholine, released during normal function. This condition leads to excitation, followed by paralysis, of the extensive peripheral and central cholinergic nervous system. Symptoms in patients experiencing OP poisonings include flushing, salivation, fasciculations, tremors, restlessness, agitation, ataxia, weakness, convulsions and coma; these symptoms develop immediately after exposure. Once the cholinergic imbalance has been corrected the neurological signs and symptoms usually disappear completely (3).

In acute OP poisonings plasma and/or red blood cell (RBC) cholinesterase activity is depressed. Plasma depression may last from one to three weeks while depression of RBC acetylcholinesterase may persist for as long as 12 weeks. If the treatment of acute organophosphate poisoning cases is inadequate, a delayed but invariably transient syndrome with similar features may appear (4).

It has been shown in animal studies that the OP anticholinergic compound, tri-o-cresyl phosphate (TOCP), can produce chronic and progressive

degeneration of lower motor neurons (5). Bidstrup et al. have suggested that the OP pesticides could produce a similar effect (6). The presence of long-term neuropsychiatric disturbances in humans following acute exposure to OP compounds has been reported by Gershon, Shaw and others (7,8). Drenth noted a high percentage of electromyogram (EMG) abnormalities among workers in OP production plants (9). Abnormal electroencephalograms (EEGs), similar to those obtained from epileptic patients, have been observed by several investigators in individuals following acute pesticide intoxications (10,11). Metcalf and Holmes (12) described less dramatic abnormalities in the EEGs after recovery from acute poisoning. Duffy et al. (13) suggested that the persistence of known short-term OP effects, when taken in conjunction with the reported long-term behavioral effects of OP exposure, provide parallel evidence that human exposure to OP compounds can culminate in brain function alterations.

In spite of the number of investigators who have reported the above findings, a number of other scientists have disagreed with these conclusions (14,15). An epidemiologic analysis of patients following acute OP intoxications did not reveal increased incidence of psychiatric disorders (16). Tabershaw and Cooper found no "serious sequela of high incidence" in patients reported as having "occupational disease attributed to organic pesticides" (17). Clark, in an extensive literature review of experimental animal studies, was unable to find consistent evidence supporting the hypotheses that exposure to OP pesticides may result in abnormal behavior (18).

Many of these clinical studies have not included epidemiologic design. For example, they have not included one or more of the following: matched

controls, complete documentation of acute exposures, sufficient quantitative measures of neurologic and behavioral functioning, and complete statistical analyses. The major objective of this epidemiologic study which was designed to overcome many of the aforementioned shortcomings, was to determine the chronic adverse health effects, if any, following an acute organophosphate poisoning.

This study was a cooperative effort of the following institutions: the Epidemiologic Pesticide Studies Center of the Institute of Rural Environmental Health of Colorado State University (Colorado Center) in Fort Collins, Colorado; the Epidemiologic Studies Program, Texas Tech University School of Medicine (Texas Program) in Lubbock, Texas; and the Departments of Neurology and Psychiatry, University of Colorado Medical Center (UCMC) in Denver, Colorado. The Colorado Center served as coordinator on the project.

MATERIALS AND METHODS

The study population consisted of 100 individuals (cases) who had previously experienced acute poisoning from OP pesticide exposures. Each case was carefully matched by age, sex, race, occupation, and educational level to a control participant. Participants in the control cohort had not experienced organophosphate poisonings. The study was specifically designed to detect any chronic neurological or neuropsychological effects in the case participants.

Case Participants. A roster of potential case participants was compiled from various health data records available in Colorado and Texas. The Colorado roster consisted of approximately 443 organophosphate pesticide poisoning cases, all of which occurred from 1950 through 1976. Holmes (19), and Savage, et al. (20) and other investigators have reported on a number of pesticide poisoning cases that occurred in Colorado. Gallaher (21) and Hatcher and Wiseman (22) and other investigators have reported on poisoning

cases from the Rio Grande Valley in Texas. The potential case participant roster in Texas consisted of about 400 individuals who had experienced acute pesticide exposures from 1960 through 1976. After screening both the Colorado and Texas rosters for completeness of poisonings documentation, a revised roster of approximately 303 potential OP poisoned participants was developed, and exhaustive attempts were made to locate all of the potential participants. Of the 303 potential participants, a total of 200 (approximately 66%) were located.

The potential participants were carefully screened for acceptance. The screening process criteria included: 1) a documented history of at least one OP poisoning; 2) diagnosis by a physician including symptoms consistent with OP poisoning; 3) a minimum age of 16 years at the time of follow-up contact; and 4) an understanding of the English language sufficient to complete the neuropsychological test. Participants were excluded if they had any of the following in their medical histories: 1) organophosphate poisonings within three months prior to testing; 2) diseases or injuries to the central nervous system including periods of unconsciousness totaling more than 15 minutes; 3) congenital defects of the central nervous system; or 4) alcohol, drug, or narcotic abuse.

Of the 200 potential participants that were located, a total of 12 (6%) were deceased; 47 persons (23.5%) did not meet the screening process criteria; and 27 (13.5%) declined to participate in the study. The remaining 114 potential case participants agreed to participate in the study. Of these, a total of 100 case participants completed the study. Examination scheduling difficulties such as great travel distances and conflicting work requirements prevented 14 cases from participating during the time period of the study.

Selection of Matched Pair Control Participants. Control participants were selected and matched to corresponding case participants with respect to age, sex, race, level of education, occupational class, social position, and ethnic background. Controls were identically matched for sex and race, and in the case of Mexican Americans, for ethnic background. Age was matched to within one year for participant ages 16 through 20; two years for ages 21-23; three years for ages 24-25; and five years for ages 26 through 70. The age matching criteria were established to be compatible with normal performance curves on the neuropsychological test battery. Persons younger than 15 were excluded from the study because the adult neuropsychological test battery is not appropriate for them, and persons older than 70 were excluded because more extreme "normal aging" effects on neuropsychological performance would be expected for such subjects.

Education, occupation, and social position were matched within one level based on scales prescribed by the Hollingshead Two Factor Index of Social Position (23). The educational scale was divided into seven levels with the highest level of educational achievement scored as 1 and the lowest level scored as 7. The occupational scale was also divided into seven levels with the highest level of occupational achievement scored as 1 and the lowest as 7. The social position index was composed of five levels with a score of 1 representing the highest level.

The control cohort participants were recruited primarily from the state of Colorado and from the Lower Rio Grande Valley of Texas. A total of 35 participants were recruited through referrals from case and control participants; 24 controls were recruited through rosters of employees furnished by businesses and public agencies; 37 participants were recruited through investigator solicitation; and in 4 cases recruitment reference source data

were incomplete. The controls were also screened to make certain they did not have histories of drug or alcohol abuse and that they had not previously experienced CNS injuries.

Participant Interview. Specially trained field epidemiologists interviewed the matched pair case and control cohorts. The interview form (Appendix A) included: demographic data, informed consent form, occupational history, pesticide exposure history, OP poisoning history (for cases) and an abbreviated medical history. In addition, the spouse or a close relative completed a questionnaire rating the participant's personality and several functioning tests. The physical, neurological and neuropsychological examinations were usually scheduled at the conclusion of the interviews.

Quality Control Assurances. A continuous effort was made to conduct the study in Colorado and Texas in a similar manner. Two field epidemiologists from the Texas Program worked with their counterparts at the Colorado Center to standardize interview techniques and the recording of data to insure uniformity.

The neuropsychological examiner who conducted tests on the Texas cohorts was trained and supervised by personnel from the UCMC Neuropsychological Laboratory. The physicians conducting the neurological evaluations in Texas and Colorado worked together to standardize their procedures prior to the start of the study and at intervals throughout the period of the study.

Physical exams, neurological testing and neuropsychological testing of Colorado participants were performed at UCMC in Denver, and Texas participants were evaluated at the Texas Program offices and at the office of a practicing neurologist in Brownsville, Texas. These examinations took a total of two days for each participant to complete. Since the protocol consisted of a blind study design, the participants were instructed not to reveal whether they were

a case or control to the investigators conducting the physical, neurological and neuropsychological evaluations. All participants received monetary compensation as reimbursement for their time, travel, and expenses.

Comprehensive Examination Protocol. The testing program about to be described was designed by board certified persons and other recognized experts to be comprehensive in the sectors of physical, neurological and neuropsychological examinations. The testing program received peer review and modification before starting. Generally accepted categories within these examinations were evaluated by the examiners using generally accepted objective tests wherever possible. Individual tests that were redundant, expensive, elaborate or very specific to annual diseases or states of impairment were avoided.

Pesticide Residue and Cholinesterase Testing. Blood samples were collected from the participants at the time of neurological examination. These samples consisted of a volume of 10 ml of venous blood collected in a heparinized tube for cholinesterase (ChE) assay (Appendix B) and another 10 ml of venous blood collected in a non-heparinized tube for chlorinated hydrocarbon pesticide residue analyses.

Physical Examinations. All case and control participants were given medical examinations consisting of physical examinations, neurological evaluations, electroencephalographic examinations, and neuropsychological testing. The routine physical examination consisted of complete medical histories, audiometric and ophthalmic examinations, and clinical blood evaluations. The medical histories and routine physical exams were conducted by the examining neurologist. The audiometric and ophthalmic examinations were conducted by qualified technicians. Clinical blood evaluations were performed at the hospital or office with which the examining neurologist was associated. All data were thoroughly reviewed by the neurologist at UCMC.

Although every attempt was made to screen potential case participants and controls prior to these evaluations, the results were used to detect and screen out participants with chronic diseases such as diabetes, renal failure, pernicious anemia and other conditions that may produce neurologic impairment. Although no such cases were found in the Colorado participants, a few participants were eliminated from the Texas group. Standard forms used for the physical examination are contained in Appendix D. The participants were informed of significant findings on their physical examination and, if indicated, they were advised to seek independent medical follow-up. In addition, significant findings of test results were summarized by the neurologist and given to the participant's personal physician.

Neurological Evaluation. As previously mentioned, all subjects were instructed not to reveal their status as either a case or a control participant during their neurological evaluation. The neurological history and formal review of systems were recorded on standard forms by the examining neurologist. This was followed by a neurological examination which consisted of an evaluation of mental status, cranial nerve function, motor system function, sensory system function, and tests of cerebellar function and coordination. Tests used in each of these categories are shown in Appendix D.

Electroencephalographic Examination. All study participants were subjected to a routine clinical electroencephalogram on either 8 or 16 channel instruments, manufactured by either the Grass or Beckman Companies. Electrodes were applied with paste according to the International 10-20 placement system. All tracings were recorded without patient sedation; photic stimulation and hyperventilation were done on all participants, and sleep phase recordings were obtained when possible. During the course of the waking record, all patients had nine minutes of data from four channels recorded onto a Vetter EM tape recorder for offline computer analysis. The

records were read visually in a standard clinical fashion and interpreted as either normal or abnormal; details of the activity seen were recorded on a research report form (Appendix E).

Neuropsychological Testing. The study participants were presented to the neurological technicians "blind". All subjects were administered the neuropsychological tests in approximately the same order to eliminate any bias associated with the order of test administration. Each participant's testing was completed in a single work day.

The tests consisted of the Wechsler Adult Intelligence Scale (WAIS) (24) and an expanded version of the test battery originally developed by Halstead (25) and Reitan (26). Numerous studies published over the last 30 years have shown that these tests are sensitive to focal and diffuse cerebral lesions caused by diverse neurologic conditions. Recent literature reviews are presented by Reitan and Davison (27) and Russel et al. (28).

The expanded Halstead-Reitan battery included measures of intelligence, attention, various cognitive functions, motor proficiency, sensory-perceptual functions, aphasia and related disorders, and learning and memory. An objective personality test was also given in an effort to determine whether pesticide-case participants showed increased tendencies toward psychiatric disturbances. The following are brief descriptions of the specific tests and test scores used in this study. More detailed descriptions can be found in the references provided.

Wechsler Adult Intelligence Scale (WAIS) (24): The WAIS is a well known and widely used measure of adult intelligence (29). The WAIS is also known to be sensitive to acquired brain lesions. Scores used in the WAIS include the Verbal, Performance, Full Scale IQ Values, and the scaled scores on the individual subtests (Information, Comprehension, Arithmetic, Similari-

on the individual subtests (Information, Comprehension, Arithmetic, Similarities, Digit Span, Vocabulary, Digit Symbol, Picture Completion, Block Design, Picture Arrangement, and Object Assembly).

Halstead Category Test (25,30): This is a relatively complex nonverbal test of abstraction and concept formation. The subject's goal in the first six subtests is to determine a unifying principle that, when applied to each item on the subtest, would give the correct answer. A seventh subtest is a review group where the subject tries to remember the answer to items seen in the earlier subtests. The score is determined by the number of errors on the total of 208 items.

Tactual Performance Test (25,30): In this test there are three trials in which the subject is blindfolded and asked to place ten geometrically shaped blocks into their correct spaces on a form board. The first trial is done with the dominant hand, trial two with the nondominant hand, and on the third trial both hands are used. The three trials are timed, and a maximum of ten minutes is alloted for each trial. The measure used to reflect psychomotor problem solving efficiency is the time (minutes) taken per block for the three trials combined.

There are also two measures of incidental memory generated on the Tactual Performance Test. The subject is not told in advance to remember anything about the blocks or the board. However, after the three trials are completed the board is removed, the blindfold is taken off, and the subject is asked to draw a picture of the form board from memory. "Memory" points are earned for correctly recalling the shapes on the board, and "location" points for shapes correctly localized on the drawing. A maximum of ten points is possible on each of the measures.

Speech Sounds Perception Test (25,30): This test requires sustained attention, accurate perception of verbal auditory stimuli, and the ability

to match simple spoken words with their written versions on an answer sheet. Sixty nonsense words are presented from a tape recorder, each having a middle "ee" vowel sound and different consonant combinations at either end. Each of the 60 spoken nonsense words must be selected (underlined) from among 4 written alternatives on the answer sheet. The score recorded is the number of errors made on the 60 items.

Seashore Rhythm Test (25,30,31): This test requires sustained attention, fine discrimination among nonverbal auditory stimuli, plus short-term memory for such stimuli. The subject is presented 30 pairs of rhythms via a tape recorder, and for each pair, is required to indicate whether the second rhythm is the same or different than the first rhythm. The score recorded is the number of correct judgments out of a possible 30.

Finger Oscillation Test (25,30): This test of upper extremities' motor speed requires the subject to tap as fast as possible with the index finger, using an apparatus which resembles a telegraph key. The mean number of taps on five 10-second trials is recorded for each hand, and in this study these two fingers are summed to give a final measure of tapping speed.

Halstead Impairment Index (25,30): In current practice, this summary measure of generalized neuropsychological deficit uses seven of the test scores described above: Category; Tactual Performance Test Total Time, Memory, and Location: Seashore Rhythm; Speech Sounds Perception; and Finger Oscillation with the dominant hand only. The index is the proportion of scores on these tests which is in the range characteristic of patients with documented cerebral lesions. Higher index scores increase the probability of impaired cerebral functioning.

Trail Making Test, Part B (30,32): This paper-and-pencil test requires general alertness, spatial analysis, motor speed, and the ability to follow

correct sequences of numbers and letters in an alternating fashion. The score is determined by the number of seconds taken to complete the test.

Aphasia Screening Examination (30,33): This is Reitan's modified version of the Halstead-Wepman aphasia screening test (34). This test is designed to screen for deficits in the participant's ability to: name common objects; spell simple words; identify letters and numbers; read and write simple words and short statements; enunciate; repeat a short statement and explain its meaning; work simple mathematical problems; demonstrate the use of a common object such as a key; and discriminate right from left. A total aphasia score, which can range from 0 to 75, was derived from the scoring and item weighing system of Russell et al. (28).

Spatial Relations (28): This is a measure of constructional dyspraxia, or degree of spatial distortion apparent in the subject's reproductions of geometric designs. The score is based upon the subject's drawing of the Greek cross from the aphasia screening exam and his scaled score on the WAIS block design subtest (28,33).

Reitan-Klove Sensory Perceptual Examination (30): During this examination, tests are administered for finger tip number writing imperception (graph-esthesia), tactile finger recognition errors (finger dysgnosia), and sensory suppressions (tactile, auditory, and visual extinction phenomena). For each test, all error scores for both sides of the body are totaled to provide a total perceptual error score.

Average Impairment Rating (28): This score is the average of the ratings, which range from 0 (better than average) to 5 (severely impaired), received by the participant on 11 of the Halstead-Reitan battery tests described above and 1 WAIS measure. The Average Impairment Rating differs from the Halstead Impairment Index in that the former includes more tests

and reflects the degree of overall impairment rather than the range of abilities affected.

Reitan-Klove Tactile Form Recognition (30): This test of stereognosis requires the study participant to discriminate among four flat plastic shapes by touch alone. A vertically positioned board is used, in which copies of the shapes are mounted on the board. The score is derived from the time (seconds) taken to complete 16 trials (8 trials with each hand).

Smedley Hand Dynamometer: This test of grip strength is often included in the Halstead-Reitan battery for clinical and research investigations (27). Two trials are given with each hand, and the average strength for each trial is recorded in kilograms (kg). The final score is the sum of the mean scores.

Klove-Matthews Motor Steadiness Battery (27): The grooved pegboard test and the hole-type steadiness test are used in this study. The grooved pegboard (Lafayette Instrument Co., No. 32035) measures speed and fine motor coordination with the upper extremities. This test requires the subject to place 25 small metal pegs into holes on a horizontal board as quickly as possible. The holes have grooves on one side, so the pegs will not fit unless they are positioned properly. A trial is given with each hand. The number of seconds taken to place all 25 pegs are recorded and totaled. The hole-type steadiness test (Lafayette Instrument Co., No. 32011) is a test of static steadiness. The study participant is asked to hold a stylus in the center of six successively smaller holes, trying not to let the stylus touch the sides. The stylus is connected to a recorder. Both hands are tested for all six holes, and error scores are totaled for the 12 trials.

Peabody Individual Achievement Test (35): The Reading Recognition, Reading Comprehension and Spelling subtests are administered to provide coverage of these academic skills. Percentile scores are used.

Thurstone Word Fluency Test (36): In Part A of this written fluency test, the study participant is given five minutes to write as many words as possible that begin with the letter "S". In Part B the participant is given four minutes to write as many four letter words as possible that begin with the letter "C". The total score is the number of words written in these two trials.

Word Finding Test (37): In this test of verbal problem solving ability, the study participant attempts to guess the identity of a word from its contexts within a series of five sentences. After hearing each sentence, the participant is given five seconds to guess the word. Then the next sentences are presented successively to provide additional clues about the word. After the test is completed the participant is given a point for each time the word is correctly identified within the five-second deadline. There are 20 words, each with five trials. A maximum score of 100 is theoretically attainable.

Wisconsin Card Sorting Test (38,39): In this test of perseverative thinking, the study participant is given a deck of cards with printed figures that vary in number (one to four), shape (circle, square, triangle, cross), and color (red, green, blue, yellow). Each card in the deck is sorted to one of four stimulus cards that vary along the same dimensions. After each sort, the participant is told only "right" or "wrong". The participant is never told the correct sorting rule, which initially is set as color. As soon as the participant sorts 10 cards in a row to color, the sorting rule is changed (without warning) to shape. Any further sorts to color are counted as perseverative responses. Then, after the participant makes 10 consecutive sorts according to shape, the rule is changed (again, without warning) to number; further sorts to shape are counted as perseverative. The test proceeds in this fashion until the participant successfully sorts through six rule changes, or until 128 cards are sorted (whichever occurs first). The score is the total number of perseverative responses.

Modified Reitan Story Memory Test, Part A (40): This is a test of verbal learning and memory. During the learning phase the study participant listens to a tape recording of a short story and is asked to repeat as much of the story as possible. If the participant cannot give a minimum of 15 of the 28 pieces of information in the story, up to 4 more learning trials are given to reach this criterion. Memory testing for the story is done four hours after the learning phase is completed. Efficiency of learning is operationally defined as the number of learning trials necessary to reach the above criterion. The memory score is the percent change in the amount of information reported at the last learning trial and the amount of information recalled four hours later.

Minnesota Multiphasic Personality Inventory (MMPI): The MMPI provides objective measures of major dimensions of psychopathology: Hypochondriasis; depression; hysteria; psychopathic deviance; paranoia; psychasthenia; schizophrenia; and mania (41,43).

Each participant and an adult relative were asked to independently rate the participant's functioning with respect to many abilities, objectively assessed by the neuropsychological test battery. These independent ratings were completed using questionnaires developed by the staff at the UCMC Neuropsychology Laboratory. Although these rating scores were not expected to be as sensitive as standardized laboratory tests, the rating scores were included to provide additional evaluation of the participants' everyday functioning, as perceived by the participants themselves and by their close relatives.

Statistical Analysis. As previously described, each case was carefully matched with a control participant within each of the two geographic locations in this study. If the grouping of study participants by geographic location were ignored, the standard paired t-test would be the appropriate statistical

analysis of any single quantitative variable (for example, Average Impairment Rating or Halstead Impairment Index). Whereas matching of cases and controls was made on the basis of age, education, and socioeconomic level, differences did exist among pairs with respect to age, education, and socioeconomic level. Such differences were important in order to avoid limitations of the study to a restricted age, education, or socioeconomic group.

The statistical analysis appropriate for the study design was an analysis of variance procedure typically referred to as a split-plot analysis but, in this study, more appropriately called a "split-pair" analysis (44). If differences in age and education were to exist among the Colorado and Texas participants, then geographic location would be a potential source of variation.

Correlation coefficients were calculated for the primary neuropsychological scores relative to the plasma and RBC cholinesterase values and the total organochlorine pesticide residues.

Data from the comprehensive neurological examination were qualitative in that the results of each specific neurological test were typically recorded as "normal" or "abnormal". For some neurological tests, the results were classified in more than two categories. Because of the matching of cases with controls in this study, the proper unit for statistical analysis was the matched pair rather than the individual case. Thus, in the case of a dichotomous outcome, the appropriate statisitcal test was McNemar's chi-square test rather than the usual unpaired chi-square test (45). In the case of a polychotomous outcome, the Stuart chi-square test for matched-pairs was applied (46).

In addition to the analysis of variance of each neuropsychological score, the set of 34 neuropsychological variables (i.e., the subtests from the WAIS,

Halstead-Reitan, Peabody, and Added Ability batteries) were analyzed simultaneously via a multivariate analysis of variance procedure for matched-pairs designs (47). To further evaluate differences between the case and control cohorts, each of the above four batteries of neuropsychological tests were statistically analyzed via the same multivariate analysis of variance procedure.

RESULTS

Demographic Data. The study population consisted of 100 matched pairs (41 pairs from Colorado and 59 pairs from Texas). Except for one pair, all study participants belonged to the white race. With respect to ethnic group there were 14 pairs of Mexican-Americans (6 pairs from Colorado and 8 pairs from Texas). Most of the Mexican-American study participants belonged to the agricultural labor force.

All of the participants were male except one matched pair of females. It was anticipated at the start of the study that a number of female pairs would be recruited; although it was never a goal of the study to study sex differences. However, only one female pair could be recruited for the study.

Ninety-six percent of the organophosphate pesticide poisonings were occupationally related, and four percent were nonoccupationally related. The occupations of the cases are summarized in Table 1. Agricultural aircraft mixers-loaders-flagmen, accounted for 38 of the 96 occupationally related cases; agricultural aircraft pilots and mechanics accounted for 19 of the cases; formulating plant employees, 13; farmers and ranchers, 11; agricultural specialty workers (greenhouse, nursery and ornamental plant workers and horticulturalists), 7; and farm laborers and field workers, 4. No pest control operators were among the cases studied. Of the four cases non-

Table 1. Occupations of organophosphate pesticide poisoning cases. Neuro-organophosphate Study, 1979.

Occupational Group	Colorado	Texas	Total
Occupationally Related Cases			
Formulating Plant Worker	9	4	13
Agricultural Chemical Sales	0	1	1
Commercial Applicator Related	0	0	0
Aircraft Mixer-Loader, Flagger	11	27	38
Pest Control Operators (PCOs)	0	0	0
Aircraft Spray Pilot, Mechanic	2	17	19
Ground Sprayer Crew	2	0	2
Farmer/Rancher	6	5	11
Agricultural Worker - Misc. Related	1	0	1
Farm Laborer, Field Worker	2	2	4
Greenhouse Operator, Nursery-Ornamental Worker, Horticulturist	6	1	7
Non-occupationally Related Cases			
Child	1	1	2
Machinist	1	0	1
Student	0	1	1
		TOTAL	100

occupationally related, two were children at the time of poisoning, one was a machinist, and the fourth was a college student.

Table 2 presents the age means and standard deviations for the case and control study cohorts. The mean age for all participants at the time of the study was approximately 35 years. The difference between the age means for the study and control participants was approximately four months. The mean age for the participants from Colorado was 39 years; the participants from Texas were somewhat younger. The age of the study participants ranged from 16 to 66.

Table 2. Age means and standard deviations (S.D.) of all study participants*. Neuro-organophosphate Study, 1979.

		Cases	Controls	Cases and Controls
All Participants	Mean	35.01	35.28	35.15
	S.D.	12.53	13.02	12.75
Colorado Participants	Mean	38.85	39.20	39.02
	S.D.	12.02	12.28	12.08
Texas Participants	Mean	32.34	32.56	32.45
	S.D.	12.28	12.92	12.55

*Data is based on age at time of physical and neurological examinations.

A summary of the Hollingshead Index of Social Position, a function of both education and occupation, is shown in Table 3. The mean value calculated for all participants was 3.05. Although the mean Hollingshead social class value fell within the lower middle class scale, the Hollingshead values for the matched pairs represented a much wider range of social class positions.

As measured by the Hollingshead Index, Colorado participants were from a slightly lower social class position than Texas participants. The age and Hollingshead Index of Social Position are listed for the 100 matched pairs in the study in Table 4.

Table 3. Mean Hollingshead social class and standard deviation (S.D.) of case and control participants*. Neuro-organophosphate Study, 1979.

		Cases	Controls	Cases and Controls
All Participants	Mean	3.22	2.88	3.05
	S.D.	1.50	1.71	1.61
Colorado Participants	Mean	3.15	3.44	3.29
	S.D.	1.59	1.16	1.39
Texas Participants	Mean	3.27	2.49	2.88
	S.D.	1.45	1.92	1.74

*Data is based on age at time of physical and neurological examinations.

Table 4. Age and Hollingshead social position scales for study participants by matched pairs. Neuro-organophosphate Study, 1979.

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position			
			Education Scale	Occupation Scale	Index Score	Social Class
1	Case	36	5	5	55	IV
	Control	34	4	5	51	IV
2	Case	36	2	3	29	III
	Control	32	1	3	25	II
3	Case	57	5	4	48	IV
	Control	52	3	4	40	III
4	Case	37	2	2	22	II
	Control	35	4	2	30	III
5	Case	40	5	3	41	III
	Control	39	4	4	44	IV
6	Case	40	1	1	11	I
	Control	45	1	1	11	I
7	Case	46	3	2	26	III
	Control	42	3	2	26	III
8	Case	47	3	3	33	III
	Control	45	3	4	40	III
9	Case	54	6	3	45	IV
	Control	55	4	5	51	IV
10	Case	40	3	4	40	III
	Control	40	3	3	33	III
11	Case	45	4	2	30	III
	Control	49	4	2	30	III
12	Case	23	5	5	55	IV
	Control	24	4	6	58	IV
13	Case	43	5	3	41	III
	Control	45	6	3	45	IV
14	Case	40	4	3	37	III
	Control	42	3	3	33	III
15	Case	36	4	4	44	IV
	Control	33	5	5	55	IV

Table 4. (Continued)

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position: Education Scale	Occupation Scale	Index Score	Social Class
16	Case	39	3	5	47	IV
	Control	42	3	4	40	III
17	Case	25	4	5	51	IV
	Control	28	4	4	44	IV
18	Case	55	2	3	29	III
	Control	56	2	3	29	III
19	Case	25	4	6	58	IV
	Control	26	4	6	58	IV
20	Case	52	2	2	22	II
	Control	53	3	3	33	III
21	Case	62	6	7	73	V
	Control	66	6	5	59	IV
22	Case	41	4	4	44	IV
	Control	44	4	3	37	III
23	Case	19	4	7	65	V
	Control	19	4	7	65	V
24	Case	57	3	4	40	III
	Control	57	3	3	33	III
25	Case	35	2	4	36	III
	Control	34	3	3	33	III
26	Case	39	6	5	59	IV
	Control	44	6	6	66	V
27	Case	22	3	7	61	V
	Control	23	3	5	47	IV
28	Case	39	3	5	47	IV
	Control	39	3	5	47	IV
29	Case	38	7	7	77	V
	Control	40	7	7	77	V
30	Case	18	4	7	65	V
	Control	19	4	7	65	V

Table 4 . (Continued)

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position: Education Scale	Occupation Scale	Index Score	Social Class
31	Case	36	6	6	66	V
	Control	35	6	4	52	IV
32	Case	19	4	6	58	IV
	Control	19	4	6	58	IV
33	Case	44	4	4	44	IV
	Control	46	4	5	51	IV
34	Case	48	4	4	44	IV
	Control	44	4	4	44	IV
35	Case	23	4	5	51	IV
	Control	22	4	6	58	IV
36	Case	36	2	2	22	II
	Control	34	3	3	33	III
37*	Case	19	4	4	44	IV
	Control	20	4	4	44	IV
38	Case	46	5	6	62	V
	Control	45	4	7	65	V
39	Case	48	1	1	11	I
	Control	48	2	2	22	II
40	Case	26	4	3	37	III
	Control	26	4	5	51	IV
41	Case	62	4	5	51	IV
	Control	64	4	5	51	IV

* Female pair.

Table 4. (Continued)

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position			
			Education Scale	Occupation Scale	Index Score	Social Class
42	Case	54	3	3	33	III
	Control	60	4	5	51	IV
43	Case	36	1	1	11	I
	Control	33	1	1	11	I
44	Case	22	4	5	51	IV
	Control	23	4	5	51	IV
45	Case	22	4	5	51	IV
	Control	25	4	5	51	IV
46	Case	49	5	3	41	III
	Control	48	4	5	51	IV
47	Case	21	4	5	51	IV
	Control	22	4	7	65	V
48	Case	50	4	4	44	IV
	Control	48	4	4	44	IV
49	Case	51	1	2	18	II
	Control	54	2	3	29	III
50	Case	27	2	3	24	II
	Control	29	2	3	29	III
51	Case	47	1	1	11	I
	Control	53	1	2	18	II
52	Case	27	5	5	55	IV
	Control	29	3	6	34	III
53	Case	16	5	7	69	V
	Control	17	5	7	69	V
54	Case	35	1	1	11	I
	Control	35	1	1	11	I

Table 4. (Continued)

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position			
			Education Scale	Occupation Scale	Index Score	Social Class
55	Case	53	7	2	42	III
	Control	54	4	3	37	III
56	Case	34	3	5	47	IV
	Control	31	3	2	26	II
57	Case	26	4	6	58	IV
	Control	26	3	7	61	V
58	Case	26	2	4	36	III
	Control	24	2	3	29	III
59	Case	22	6	5	59	IV
	Control	20	6	6	66	V
60	Case	25	3	4	40	III
	Control	26	4	6	58	IV
61	Case	23	3	5	47	IV
	Control	23	4	5	51	IV
62	Case	36	2	3	29	III
	Control	36	3	4	40	III
63	Case	27	3	3	33	III
	Control	29	3	3	33	III
64	Case	29	4	3	37	III
	Control	32	4	6	58	IV
65	Case	39	4	4	44	IV
	Control	42	4	2	30	III
66	Case	25	3	5	47	IV
	Control	25	3	3	33	III
67	Case	31	3	5	47	IV
	Control	30	3	3	33	III

Table 4. (Continued)

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position: Education Scale	Occupation Scale	Index Score	Social Class
68	Case	19	4	7	65	V
	Control	19	5	6	62	V
69	Case	47	6	4	52	IV
	Control	47	5	6	62	V
70	Case	27	4	6	58	IV
	Control	24	2	4	36	III
71	Case	25	3	3	33	III
	Control	25	3	4	40	III
72	Case	28	5	6	62	V
	Control	32	3	7	61	V
73	Case	17	5	7	69	V
	Control	17	5	7	69	V
74	Case	27	2	4	36	III
	Control	27	2	3	29	III
75	Case	27	4	5	51	IV
	Control	28	4	5	51	IV
76	Case	22	3	4	40	III
	Control	21	3	4	40	III
77	Case	23	5	6	62	V
	Control	24	7	7	77	V
78	Case	26	4	4	44	IV
	Control	28	3	3	33	III
79	Case	17	4	5	51	IV
	Control	17	4	7	65	V
80	Case	20	6	5	59	IV
	Control	19	5	7	69	V

Table 4. (Continued)

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position			
			Education Scale	Occupation Scale	Index Score	Social Class
81	Case	22	3	3	33	III
	Control	23	2	2	22	II
82	Case	19	5	5	55	IV
	Control	18	4	7	65	V
83	Case	29	2	2	22	II
	Control	28	2	2	22	II
84	Case	56	4	4	44	IV
	Control	55	3	3	33	III
85	Case	50	4	7	65	V
	Control	51	4	5	51	IV
86	Case	52	2	3	29	III
	Control	53	2	1	15	I
87	Case	55	3	3	33	III
	Control	56	3	2	26	II
88	Case	47	3	3	33	III
	Control	48	3	4	40	III
89	Case	26	3	5	47	IV
	Control	27	3	4	40	III
90	Case	64	3	3	33	III
	Control	66	4	3	37	III
91	Case	56	4	4	44	IV
	Control	57	3	7	61	V
92	Case	31	2	3	29	III
	Control	26	2	2	22	II
93	Case	23	4	5	51	IV
	Control	22	3	7	61	V

Table 4. (Continued)

Study Pair No.	Case or Control	Age at Interview	Hollingshead Social Position			
			Education Scale	Occupation Scale	Index Score	Social Class
94	Case	29	3	4	40	III
	Control	29	2	2	22	II
95	Case	29	2	1	13	I
	Control	32	2	2	22	II
96	Case	27	3	5	47	IV
	Control	25	3	5	47	IV
97	Case	22	4	5	51	IV
	Control	20	4	5	51	IV
98	Case	28	3	5	47	IV
	Control	25	3	4	40	III
99	Case	34	3	5	47	IV
	Control	34	4	5	51	IV
100	Case	27	4	7	65	V
	Control	29	4	3	37	III

Acute Organophosphate Pesticide Poisoning Histories. The year of the primary OP pesticide poisoning reported by the case participants ranged from 1950 to 1976. There were 11 participants in the case cohort who reported more than one noteworthy OP pesticide poisoning: eight of these experienced two poisonings, one experienced three poisonings, and two reported four poisonings. One case reported a poisoning as early as July 1948. Documentary information usually was not available on the multiple poisonings other than for the primary incident.

The mean time for all cases from the primary poisoning to the time of the neurological and neuropsychological examinations was about nine years. The time from the index poisoning incident to the date of the neurological and psychological examinations is important because examination close to the time of poisoning could be measuring adverse results which were, in fact, reversible acute poisoning responses rather than long-term effects. The elapsed time from the last poisoning case to the date of neuropsychological examination is given in Table 5 below for the case cohort. There was a longer mean elapsed time for the Colorado cases, 4228 days (about 11 years, 7 months) than for the Texas cases, 2574 days (about 7 years, 19 days). The mean elapsed time from the date of the last poisoning case to neuropsychological

Table 5. Elapsed time in days from last poisoning to neuropsychological examination. Neuro-organophosphate Study, 1979.

	Number of Cases	Range	Mean
All cases	100	117-9640	3252
Colorado	41	650-8065	4228
Texas	59	117-9640	2574

testing for all cases was 3252 days (about 8 years, 11 months). The shortest time period from date of poisoning to date of examination was 117 days. It is of interest that the RBC and plasma cholinesterase values on this person were well within the normal range at the time of the study examinations.

Among the 100 case participants, 10 different OP pesticides were implicated as the cause of the primary poisoning (Table 6). Detailed information on these chemicals, such as chemical structure, toxicity, and uses is given in Appendix F. Methyl parathion was implicated in 54 cases, more than any other chemical; ethyl parathion was implicated in 42 poisonings. These two chemicals accounted for 79% of the total episodes. The two chemicals are very similar in structure, toxicological effects, in practical field use, and sometimes they are applied in combination. Their predominance as a cause of human poisoning may be explained by the fact that they have been in use for a number of years, are highly toxic, and are among the most widely used pesticides in the United States. All of the incidents involving methyl parathion were among the Texas case participants, whereas ethyl parathion was involved in poisonings in both Colorado and Texas.

Physical Examination and Clinical Laboratory Data. Abnormalities detected during the physical examinations were recorded on the physical exam forms (Appendix D). Table 7 summarizes the findings of the physical examination of case and control participants. Abnormalities were observed by the examining physicians in 11 of the 15 categories on the physical examination forms. Slightly more abnormalities were observed among the controls (48) than among the cases (44), but the difference was not statistically significant.

Table 6. Organophosphate pesticides implicated in the primary poisoning incidents*. Neuro-organophosphate Study, 1979.

OP Pesticide	Number of Cases		
	Colorado	Texas	Total
Methyl parathion	0	54	54
Parathion	24	18	42
Disulfoton (Di-Syston)	8	0	8
Malathion	6	0	6
Mevinphos (Phosdrin)	5	0	5
Dicrotophos (Bidrin)	1	1	2
TEPP	1	1	2
Dioxathion (Delnav)	0	1	1
DEF	0	1	1
Phorate (Thimet)	1	0	1
TOTAL			122

*The occurrence of OP pesticides exceeds the number of cases in the study because more than one OP pesticide was implicated in some incidents.

Table 7 . Summary of abnormal conditions identified in participants during physical examination. Neuro-organophosphate Study, 1979.

Category	n = 98 pairs		
	Cases	Controls	Total
General appearance	3	1	4
Skin	10	11	21
Head	0	0	0
Ears	2	0	2
Eyes	3	4	7
Nose	0	0	0
Mouth	0	0	0
Neck	0	0	0
Thorax	0	1	1
Breasts	1	0	1
Lungs	7	7	14
Heart	2	4	6
Vessels	3	6	9
Abdomen	2	4	6
Skeletal	11	10	21
Total	44	48	92

Skin and skeletal were the two most frequently recorded abnormalities as each abnormality was observed 21 times. Abnormalities in the category of the lungs was the third highest and occurred in 7% of the participants. Abnormal breath sounds was the dominant finding among the lung abnormalities. The frequency of occurrence of abnormalities in the other categories were varied and no abnormalities were found in four categories. However, the slight differences between cases and controls with respect to the physical examination categories were not statistically significant.

Although no participants were excluded from the study due to physical, audiometric, ophthalmic, or clinical blood examination results, three potential participants were excluded from the study because of previous medical conditions identified during the medical history taken by the examining physician.

Clinical Laboratory Results. The blood samples collected from the study participants were evaluated using standard laboratory tests (Appendix D). The results of 28 different laboratory tests were recorded for each participant. Results were recorded as normal and abnormal. Statistical analysis of the hematology, creatinine, and urea nitrogen test results were based on the chi-square test for matched pairs, as described in the Methods section. None of these chi-square tests were statistically significant (Table 8).

Neurological Data. The neurological testing was an important aspect of this study and included two categories: neurological examinations and the electroencephalographic examinations. The neurological examinations shown in Appendix D consisted of the following general categories: mental status, cranial nerves, motor system, sensory system, integrative functions and other.

The electroencephalogram (EEG) is a relatively subtle indicator of structural and functional integrity of the cerebral cortex. Evaluation of

Table 8. Summary of the statistical comparison of the cases and controls with respect to selected laboratory test variables. Neuro-organophosphate Study, 1979.

Test Variable	Degrees of Freedom	Chi-square Statistic	p-Level
Lab Tests			
White blood cells	2	2.00	.368
Red blood cells	2	.80	.670
Hemoglobin	2	2.82	.244
Hematocrit	2	3.27	.195
Lymphocytes	2	.04	.980
Eosinophiles	1	1.23	.267
Urea nitrogen	2	2.14	.343
Creatinine	2	1.93	.381

the EEG is usually a subjective process depending on pattern recognition by the electroencephalographer. Recognition and descriptions of specific patterns are often based on scientific intuition. The EEG has been an important tool in determining overall cortical function in many clinical and research situations.

Based on the visual analysis of EEG, as well as the descriptive interpretation of the EEG, each study participant's EEG results were categorized as normal or as abnormal (mild, moderate or severe). A summary of the results of the encephalograms are shown in Table 9. Statistical analyses of the electroencephalogram results yielded a 1.06 chi-square value ($p = .589$, with 2 degrees of freedom) approximately 83 per cent of the cases and 88 per cent of the controls had normal readings. Although computer spectral analyses were planned to supplement the visual interpretation, the spectral analyses were not completed due to computerization problems at the University of Colorado Medical Center.

Table 9. Summary of the results of the encephalogram (EEG) evaluation of case and control participants. Neuro-organophosphate Study, 1979.

	Abnormal			
	Moderate	Mild	Normal	Total
Cases	2	14	83	99
Controls	1	10	88	99

The neurological exam was divided into six general categories: Mental Status, Cranial Nerves, Motor System, Sensory System, Integrative Functions, and Other. Each of the six general categories consisted of a number of separate examination components. The components were rated and coded on the exam form by the neurologist as normal, not significant, or abnormal (Appendix 10). A summary evaluation of the separate components for each general category was similarly assigned by the neurologist.

Table 10 shows the summary of the statistical comparison of the cases and controls with respect to Mental Status, Cranial Nerves and Motor System categories. The following six tables (Tables 11-16) present a summary of the data used in calculating the chi-square values in summary Table 10.

There were several components of the overall Mental Status evaluation: State of Consciousness; Orientation; Language; Memory; Serial Subtraction; Abstraction; and Mood. The results of the neurological evaluation of these components of Mental Status are summarized in Table 11. Although the State of Consciousness results showed the cases to be more anxious than the controls, the difference between these groups was not statistically significant. With respect to Orientation (time; place; and person) and Language (Pressure and Structure), there was little or no difference between the cases and controls (Table 10). Similarly, for three parts of the Memory evaluation (Numbers Forward; Numbers Backward; and Remote Memory), the difference between cases

and controls was not statistically significant. However, one part of the Memory component (Three-Pairs-of-Item) showed over twice as many abnormal classifications in the cases as in the controls ($p = .006$). Based on the matched-pairs analysis, there was no significant difference between the cases and controls in Serial Subtraction component. Of the ten abnormal classifications in the Abstraction component, nine belonged to the case cohort ($p = .028$). The neurological evaluation of Mood is an important aspect of Mental Status. It is of considerable interest that six of the case participants and none of the control participants were classified as "depressed" ($p = .0003$). Based on the neurologist's summary evaluation of Mental Status, 64 of 99 case participants and 45 of 99 control participants were categorized as abnormal. The matched-pairs analysis found this difference between the two cohorts to be highly significant ($p = .013$).

The summary evaluation of the Cranial Nerve category showed no significant difference between the case and control participants (Table 10). The individual components of the Cranial Nerve category, such as Bilateral Neurosensory Hearing, Eye Mobility and Sense of Smell, were not found to be significantly different between the two cohorts. Table 12 shows that 64 cases and 59 controls were evaluated as normal on the Cranial Nerve summary.

Twenty-three components (Appendix D) were considered by the neurologist in the evaluation of the Motor System. Although the difference in summary evaluations for the case and control cohorts was not statistically significant, (Table 10), some of the individual components were significantly different. For example, in the knee jerk test, the case cohort was significantly different from the control cohort ($p = .024$). However, in the ankle jerk test, the difference between the case and control cohorts was not statistically significant. The data on selected components of the Motor System are presented in Tables 14 and 15 and the data on the Motor System summary evaluation are presented in Table 16.

Table 10. Summary of the statistical comparison of the cases and controls with respect to mental status, cranial nerves, and motor system. Neuro-organophosphate Study, 1979.

Test Variable	Degrees of Freedom	Chi-Square Statistic	P-Value
MENTAL STATUS			
Mental Status Summary Evaluation	1	6.35	.013
State of Consciousness	1	0.07	.791
Orientation			
Time	1	0.00	----
Place	1	0.00	----
Person	1	0.00	----
Language			
Pressure	1	0.00	----
Structure	1	0.00	----
Memory			
Numbers Forward	1	0.55	.481
Numbers Backward	1	3.03	.086
Three Pairs of Items	1	7.50	.006
Remote	1	0.00	----
Serial Subtraction	2	3.08	.290
Abstraction	1	4.90	.028
Mood	2	18.00	.001
CRANIAL NERVES			
Cranial Nerve Summary Evaluation	2	1.41	.494
MOTOR SYSTEM			
Right and Left Knee Jerk	8	17.64	.024
Right and Left Ankle Jerk	7	8.52	.289
Motor System Summary Evaluation	2	2.90	.235

Table 11. Evaluation of case and control participants with respect to the summary and components of the mental status category of the neurological examination. Neuro-organophosphate Study, 1979.

Test Variable		Abnormal	Normal	Total
Summary Evaluation of Mental Status	Cases	64	35	99
	Controls	45	54	99
Orientation				
Time	Cases	1	98	99
	Controls	0	99	99
Place	Cases	0	99	99
	Controls	1	98	99
Person	Cases	0	99	99
	Controls	0	99	99
Language				
Pressure	Cases	0	99	99
	Controls	1	98	99
Structure	Cases	0	99	99
	Controls	0	99	99
Memory				
Numbers Forward	Cases	23	76	99
	Controls	18	81	99
Numbers Backward	Cases	25	74	99
	Controls	14	85	99

Table 11 (continued)

Test Variable		Abnormal	Normal	Total
Memory (continued)				
Three Pairs of Items	Cases	30	69	99
	Controls	14	85	99
Remote	Cases	0	99	99
	Controls	0	99	99
Serial Subtraction	Cases	28	71	99
	Controls	21	78	99
Abstraction	Cases	9	90	99
	Controls	1	98	99

Table 12. Evaluation of case and control participants with respect to the state of consciousness and mood from the mental status category of the neurological examination. Neuro-organophosphate Study, 1979.

Test Variable		Anxious	Normal	Total
State of Consciousness				
	Cases	8	91	99
	Controls	6	93	99

Mood		Euphoric	Depressed	Normal	
	Cases	1	6	92	99
	Controls	0	0	99	99

Table 13. Evaluation of case and control participants with respect to the cranial nerve category summary evaluation of the neurological examination. Neuro-organophosphate Study, 1979.

		Abnormal		
	Normal	Nonsignificant	Significant	Total
Cases	64	9	26	99
Controls	59	7	33	99

Table 14. Evaluation of case and control participants with respect to the knee jerk (right and left combined) test of the neurological examination. Neuro-organophosphate Study, 1979.

	One 0 Other 0	One 0 Other 1	One 1 Other 1	One 1 Other 2	One 2 Other 2	Total
Cases	2	1	75	9	10	95
Controls	2	6	64	9	16	97

0 = Absent
1 = Normal
2 = Hyperactive

Table 15. Evaluation of case and control participants with respect to the ankle jerk (right and left combined) test of the neurological examination. Neuro-organophosphate Study, 1979.

	One 0 Other 0	One 0 Other 1	One 1 Other 1	One 1 Other 2	One 2 Other 2	Total
Cases	3	10	75	1	8	97
Controls	6	10	67	0	14	97

0 = Absent
1 = Normal
2 = Hyperactive

Table 16. Evaluation of case and control participants with respect to the motor system score test of the neurological examination. Neuro-organophosphate Study, 1979.

		Abnormal		
	Normal	Nonsignificant	Significant	Total
Cases	61	8	30	99
Controls	54	16	29	99

The sensory system was further evaluated through a series of 10 additional clinical tests. The tests included response to pin pricks, touch, vibration, position identification, discrimination, graphesthesia, and stereognosis (Appendix D). Table 17 summarizes the results of the statisitical analyses of the sensory system tests and the sensory system summary score. There were no statistically significant differences between the case and control cohorts on any of these tests or on the sensory system summary evaluation. Tables 18-24 present the summary results of the sensory system tests. Analyses showed there were slight differences in the pin prick lower left extremity where a total of 96 controls were normal compared to 89 cases that were normal (Table 21), but the results were not statistically significant ($p = .072$).

Table 17. Summary of the statistical comparison of the cases and controls with respect to the sensory system. Neuro-organophosphate Study, 1979.

Test Variable	Degrees of Freedom	Chi-Square Statistic	p-Level
SENSORY SYSTEM			
Pin Upper Right Extremity	5	5.20	.392
Pin Upper Left Extremity	5	8.00	.156
Pin Lower Right Extremity	3	3.20	.362
Pin Lower Left Extremity	3	7.00	.072
Vibration, Right	4	5.10	.277
Vibration, Left	5	4.03	.545
Sensory System Evaluation	2	3.54	.170

Table 18. Evaluation of case and control participants with respect to the pin upper right extremity test of the neurological examination. Neuro-organophosphate Study, 1979.

		Peripheral			Focal			
	Normal	Mild	Moderate	Severe	Mild	Moderate	Severe	Total
Cases	94	0	1	1	2	0	0	98
Controls	92	2	0	0	3	1	0	98

Table 19. Evaluation of case and control participants with respect to the pin upper left extremity test of the neurological examination. Neuro-organophosphate Study, 1979.

		Peripheral			Focal			
	Normal	Mild	Moderate	Severe	Mild	Moderate	Severe	Total
Cases	93	0	1	1	3	0	0	98
Controls	95	2	0	0	0	1	0	98

Table 20. Evaluation of case and control participants with respect to the pin lower right extremity test of the neurological examination. Neuro-organophosphate Study, 1979.

	Normal	Peripheral			Focal			Total
		Mild	Moderate	Severe	Mild	Moderate	Severe	
Cases	91	0	2	1	3	0	0	97
Controls	95	0	0	0	2	0	0	97

Table 21. Evaluation of case and control participants with respect to the pin lower left extremity test of the neurological examination. Neuro-organophosphate Study, 1979.

	Normal	Peripheral			Focal			Total
		Mild	Moderate	Severe	Mild	Moderate	Severe	
Cases	89	0	3	1	4	0	0	97
Controls	96	0	0	0	1	0	0	97

Table 22. Evaluation of case and control participants with respect to the vibration, right test of the neurological examination. Neuro-organophosphate Study, 1979.

		Peripheral			Focal			
	Normal	Mild	Moderate	Severe	Mild	Moderate	Severe	Total
Cases	74	10	6	1	0	0	0	91
Controls	66	13	8	0	0	2	0	91

Table 23. Evaluation of case and control participants with respect to the vibration, left test of the neurological examination. Neuro-organophosphate Study, 1979.

		Peripheral			Focal			
	Normal	Mild	Moderate	Severe	Mild	Moderate	Severe	Total
Cases	70	13	5	1	2	0	0	91
Controls	65	16	6	0	2	2	0	91

Table 24. Summary evaluation of case and control participants with respect to the sensory system of the neurological examination. Neuro-organophosphate Study, 1979.

	Normal	Abnormal		Total
		Nonsignificant	Significant	
Cases	66	2	30	98
Controls	62	1	35	98

Table 25 is a summary of the matched-pairs analyses of selected integrative function tests and other miscellaneous examinations. Appendix D includes examination forms used in these tests. A total of seven individual component tests were used in the integrative function summary evaluations. These component lists included posture, balance, gait, and cerebellar functions, such as finger to nose and heel to skin. Tables 26-29 present a summary of the results of the individual component tests. The integrative function summary evaluation was normal for 77 cases and 85 controls out of 99 matched pairs ($p = .185$).

Other miscellaneous examinations included examination of the skull, carotids, and back (Appendix D). Based on the chi-square test for matched pairs (Table 25), there was no statistical difference between the case and control cohorts on the summary evaluation of other miscellaneous examinations (Table 24). As seen from Table 29, there were 98 cases and 95 controls normal on the other miscellaneous examination summary evaluation.

Table 25. Summary of the statistical comparison of the cases and controls with respect to integrative function and other miscellaneous examinations, Neuro-organophosphate Study, 1979.

Test Variable	Degrees of Freedom	Chi-Square Statistic	p-Level
Finger-nose Right	3	3.92	.270
Finger-nose Left	3	0.60	.896
Integrative Function Evaluation	2	3.38	.185
Other Misc. Exam Evaluation	2	2.00	.368

Table 26. Evaluation of case and control participants with respect to the finger-nose right test of the neurological examination. Neuro-organophosphate Study, 1979.

		Abnormal Peripheral			Abnormal Focal			
	Normal	Mild	Moderate	Severe	Mild	Moderate	Severe	Total
Cases	85	10	0	0	1	0	0	96
Controls	88	5	2	0	1	0	0	96

Table 27. Evaluation of case and control participants with respect to the finger-nose left test of the neurological examination. Neuro-organophosphate Study, 1979.

		Abnormal Peripheral			Abnormal Focal			
	Normal	Mild	Moderate	Severe	Mild	Moderate	Severe	Total
Cases	86	7	2	0	1	0	0	96
Controls	87	5	3	0	1	0	0	96

Table 28. Summary evaluation of case and control participants with respect to the integrative function of the neurological examination. Neuro-organophosphate Study, 1979.

		Abnormal		
	Normal	Nonsignificant	Significant	Total
Cases	77	2	20	99
Controls	85	0	14	99

Table 29. Summary evaluation of case and control participants with respect to other miscellaneous exams of the neurological examination. Neuro-organophosphate Study, 1979.

		Abnormal		
	Normal	Nonsignificant	Significant	Total
Cases	98	1	0	99
Controls	95	3	1	99

Neuropsychological Findings. Results of neuropsychological evaluations are presented in this section according to three subdivisions: objective tests administered in the neuropsychological laboratory; results of the participant-completed Patient Assessment of Own Functioning Inventory which was administered at the time of neuropsychological examination; and results of the Relative's Assessment of Patient-Functioning Inventory that was completed at the time of interview. As mentioned previously, these data were analyzed via an analysis of variance procedure specific to designs involving matched-pairs. The detailed results of the analysis of variance of the neuropsychological test battery and the MMPI are presented in Appendix F. These results are summarized in Tables 30-32, which present the mean score for the case and control cohorts and the probability-level (p-level) for the analysis of variance test comparing the case and control means.

Results of the Halstead-Reitan Battery revealed that the case cohort was significantly more impaired than the control cohort on both summary measures Average Impairment Rating and Halstead Impairment Index ($p < .001$ and $p = .020$, respectively). Although both of the group means are in the normal range on these measures, 24 of the cases and only 12 of the controls obtained scores in the "impaired" range on one or both of the measurements. That is, on the basis of previously validated limits (1.55 for the Average Impairment Rating and 0.5 for the Halstead Index), twice as many case participants as control participants showed an overall level of neuropsychological deficit that is within the range characteristic of individuals with documented cerebral lesions. Based on the matched-pairs chi-square analysis, this difference between the case and control cohorts was statistically significant ($p < .05$). In the Halstead-Reitan battery, the performance level of the cases was lower than that of the controls on nine of the eleven individual tests; however, the

Table 30. Psychological test score means, standard error of the difference of means, and the probability level of the analysis of variance test for the case-control comparison for the Halstead-Reitan Battery and the WAIS Battery. Neuro-organophosphate Study, 1979.

Variable	Means		S.E.	p-level*
	Cases	Controls		
Neuropsychological Summary Scores				
Average Impairment Rating	1.07	0.91	.05	<.001
Halstead Impairment Index	0.30	0.23	.03	.020
WAIS Verbal IQ	105.40	111.86	1.31	<.001
WAIS Performance IQ	108.41	110.13	1.46	.242
WAIS Full Scale IQ	107.05	111.77	1.32	<.001
Halstead-Reitan Battery				
Category	39.55	31.57	2.59	.002
Trails-B	75.31	67.72	4.09	.067
Speech Sounds Perception	7.78	5.92	.51	.001
Seashore Rhythm	26.65	27.16	.33	.120
Tactual Performance-Memory	7.62	7.78	.17	---
Tactual Performance-Location	4.57	4.45	.25	---
Tactual Performance-Time	13.07	11.88	.77	.125
Finger Oscillation Test[a]	100.80	103.69	1.41	.042
Perceptual Disorders[b]	4.68	4.17	.63	---
Aphasia Exam[b]	5.59	4.55	.58	.075
Spatial Relations[b]	2.81	2.71	.13	---
WAIS Subtest Scaled Scores				
Information	10.73	11.83	.28	<.001
Comprehension	11.32	12.13	.34	.020
Arithmetic	11.15	12.40	.32	<.001
Similarities	11.10	12.09	.31	.002
Digit Span	9.80	10.95	.43	.008
Vocabulary	10.49	11.68	.30	<.001
Digit Symbol	9.71	10.64	.26	<.001
Picture Completion	11.13	11.00	.28	---
Block Design	11.24	11.75	.38	.187
Picture Arrangement	10.02	9.95	.35	---
Object Assembly	10.60	10.72	.33	---

(a) Scores summed for both hands
(b) Ratings defined in Russell et al. (1970)
* The p-level is not shown if the F-ratio is less than unity.

Table 31. Psychological test score means, standard error of the difference of means, and the probability level of the analysis of variance test for the case-control comparison for the Peabody Individual Achievement Test and Added Ability Tests. Neuro-organophosphate Study, 1979.

Variable	Means		S.E.	p-level*
	Cases	Controls		
Peabody Individual Achievement Test				
Reading Recognition	29.00	36.71	2.32	.001
Reading Comprehension	54.32	63.06	3.26	.008
Spelling	35.19	45.81	3.65	.004
Added Ability Tests				
Tactile Form Recognition[a]	20.34	19.98	.75	----
Hand Dynamoneter[a]	96.87	97.34	1.93	----
Grooved Pegboard[a]	148.34	137.96	3.26	.002
Hole-Type Steadiness[a]	59.39	62.82	6.76	----
Wisconsin Card Sorting Test[b]	17.07	12.91	1.18	.001
Thurstone Word Fluency-Total	43.92	50.79	2.33	.003
Word Finding Test[c]	36.04	40.36	1.33	.002
Story Memory Test-Learning	1.87	1.67	.02	.045
-Memory	.11	.10	.10	----

(a) Scores summed for both hands
(b) Score available for 91 of 100 pairs
(c) Score abailable for 99 of 100 pairs
* The p-level is not shown if the F-ratio is less than unity.

Table 32. Psychological test score means, standard error of the difference of means, and the probability level of the analysis of variance test for the case-control comparison for the MMPI Battery. Neuro-organophosphate Study, 1979.

	Means		S.E.	p-level*
	Cases	Controls		
MMPI (T-Scores)				
Lie (L)	50.62	49.30	1.04	.114
Validity (F)	56.42	53.36	1.25	.008
Defensiveness (K)	50.68	54.79	1.23	.018
Hypochondriasis (Hs)	52.47	52.94	1.40	----
Depression (D)	55.72	54.28	1.57	.202
Hysteria (Hy)	54.00	57.12	1.21	.095
Psychopathic Deviate (Pd)	56.65	56.41	1.45	----
Masculinity Femininity (Mf)	56.25	55.97	1.23	----
Paranoia (Pa)	56.40	54.00	1.21	.027
Psychasthenia (Pt)	56.70	55.32	1.47	.200**
Schizophrenia (Sc)	56.02	53.45	1.57	.058**
Hypomania (Ma)	58.95	57.21	1.32	.119
Social Introversion (Si)	53.83	50.65	1.30	.050

*The p-level is not shown if the F-ratio is less than unity.
**The p-level for the F-test for interaction in the analysis of variance was significant at the 5% level of significance.

Table 32. Psychological test score means, standard error of the difference of means, and the probability level of the analysis of variance test for the case-control comparison for the MMPI Battery. Neuro-organophosphate Study, 1979.

	Means		S.E.	p-level*
	Cases	Controls		
MMPI (T-Scores)				
Lie (L)	50.62	49.30	1.04	.114
Validity (F)	56.42	53.36	1.25	.008
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Psychopathic Deviate (Pd)	56.65	56.41	1.45	----
Masculinity Femininity (Mf)	56.25	55.97	1.23	----
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Schizophrenia (Sc)	56.02	53.45	1.57	.058**
Hypomania (Ma)	58.95	57.21	1.32	.119
Social Introversion (Si)	53.83	50.65	1.30	.050

*The p-level is not shown if the F-ratio is less than unity.
**The p-level for the F-test for interaction in the analysis of variance was significant at the 5% level of significance.

group's profiles, but they do suggest that the case participants were somewhat more likely than the controls to report emotional problems on the MMPI. In addition, the case participants scored higher than the controls on the MMPI Paranoia and Social Introversion scales. These findings suggest slightly greater social anxiety and tendencies towards suspiciousness and/or sensitivity to criticism or to other social stresses among the cases.

Table 33 summarizes the results of the statistical comparisons between cohorts on the Patient Assessment of Own Functioning Inventory. Significant cohort differences were obtained on 11 of the 32 items. All of the significant differences indicated that the case cohort reported more problems with their everyday functioning than did their matched pair.

It is also of interest that there appears to be some relationship between the specific problem areas mentioned in the self-reports completed by case participants and those cases shown to be most impaired on formal objective testing in the neuropsychological laboratory. Thus, when compared to those of the controls, the patient assessment of own functioning from the case cohort disclosed somewhat more difficulty with verbal comprehension, word finding abilities, reading and math skills, general problem solving, efficiency in following directions and instructions, and manipulatory efficiency. Furthermore, the case cohort participant gave evidence of relative impairment in all of these areas of formal neuropsychological testing. By contrast, there was no difference between the case and control cohorts with respect to self-assessments of memory; this result agrees with a similar result (i.e., no significant difference) in the formal objective testing of memory abilities. The statistical results for each of 32 items used in the Patient Assessment of Own Functioning Inventory are presented in detail in Appendix G.

difference between case and control means was significant in only three of these none tests. When compared to their matched controls, the cases showed impairment on tests of logical analysis and abstract reasoning (Category Test), fine discrimination among isolated speech sounds (Speech-Sounds Perception Test), and motor speed with the upper extremities (Finger Oscillation Test); although not statistically significant, the cases showed some impairment on tests of efficiency in following sequential procedures (Trail Making Test, Part B) and language skills (Aphasia Exam). There was no difference between the two cohorts on the Sensory Perceptual Examination.

In general, both cohorts showed above average intellectual functioning on the WAIS. However, the case cohort obtained a mean Full Scale IQ that was almost five points lower than the mean of the control cohort. This difference was highly significant ($p < .001$). The case cohort also did significantly worse than the controls on all six verbal subtests and on one of the five performance subtests (Digit Symbol).

The case cohort also performed at a significantly lower level than the controls on the Reading Recognition, Reading Comprehension, and Spelling subtests of the Peabody Individual Achievement Test. Cohort differences were also significant on five of the ten "added" ability tests: tests of written verbal fluency (Thurstone Word Fluency Test), verbal problem solving ability (Word Finding Test), perserverative thinking (Wisconsin Card Sorting Test), fine motor coordination with the upper extremities (Grooved Pegboard Test), and learning (Story Memory Test-Learning). The case and control cohorts did not differ significantly in the test of memory (Story Memory Test-Memory).

Although the mean scores from the MMPI are well within normal limits for both case and control cohorts, results of four of the thirteen scales were statistically significant. The differences on the Validity (F) and Defensiveness (K) scales do not imply any problems with the validity of either

Table 33. Patient's Assessment of Own Functioning: Test Score Means, Pooled Estimate of the Standard Error (S.E.) of Each Mean, and Probability Level of the Analysis of Variance Test for the Case Control Comparison. Neuro-organophosphate Study, 1979.

	Means			
	Cases	Controls	S.E.	P-level*
Patient Self-Report: Memory				
For verbal communications in last day or two	1.95	1.77	.10	.210
For events occurring in last day or two	1.22	1.06	.11	.310
For people met in last day or two	1.46	1.30	.14	-
For things known a year or more ago	1.93	2.04	.12	-
For people met a year or more ago	1.91	1.98	.13	-
Losing track of time	1.43	1.40	.11	-
Forgetting what patient is doing	.79	.76	.10	-
Forgetting how to do things	.90	.72	.09	-
Losing things by forgetting where they are	1.98	1.95	.11	-
Forgetting obligations	1.31	1.37	.11	-
Patient Self-Report: Language and Communication				
Difficulties understanding speech of others	1.71	1.31	.11	.014
Difficulties recognizing printed or written words	1.22	.80	.11	.008
Difficulties understanding reading material	1.14	.76	.12	.024
Difficulties with enunciation	1.66	1.41	.13	.163
Difficulty thinking of names of things	2.02	1.73	.10	.037
Other word finding difficulties	1.93	1.83	.14	-
Difficulty forming letters correctly	1.28	1.05	.13	.224
Difficulty spelling	1.77	1.42	.14	.071

	Means			
	Cases	Controls	S.E.	P-level*
Patient Self-Report: Use of Hands				
Difficulty performing tasks with right hand	.69	.29	.11	.010
Difficulty performing tasks with left hand	1.21	1.29	.14	-
Patient Self-Report: Perceptual Functions				
Difficulty feeling with right hand	.26	.12	.06	.126
Difficulty feeling with left hand	.25	.27	.06	-
Difficulty with vision	.81	.48	.10	.019
Patient Self-Report: Cognitive/Intellectual Functions				
Thoughts seem confused or illogical	.96	.90	.10	-
Distracted from what doing or saying	1.23	1.01	.10	.133
Confusion about where patient is	.51	.42	.09	-
Difficulty finding way	.46	.48	.09	-
Difficulty calculating	1.05	.66	.10	.009
Difficulty planning and organizing activities	1.03	.85	.11	.241
Difficulty solving problems	.96	.69	.09	.036
Difficulty following directions	.84	.54	.10	.044
Difficulty following instructions	1.12	.69	.10	.004

*The p-level is not given in cases for which the F-ratio is less than unity.

Results of the Relative Assessment of Patient Functioning Inventory showed few significant differences between the case cohort and control cohort (see Table 34). As shown in Table 34, significant differences did occur on 4 of 30 items in the ability areas ($p < .05$). All of the significant differences measured by the relative's assessment showed that the case cohort had more difficulty in functioning than the control cohort. The difficulties were in the general areas (language and communication, cognitive and intellectual functions, and use of hands). In addition, results of the relatives' assessment of the study participants were significantly different between the case and control cohorts on 4 of the 22 personality scale items: depression, irritability, social withdrawal, and confusion. The statistical results of the individual relative's assessment evaluations are presented in detail in Appendix H.

Blood Pesticide Residues and ChE Assays. Blood samples were taken from each case and control participant at the time of their physical examination. All blood samples were analyzed for organochlorine pesticide residues and for cholinesterase depression. The results from the residue analyses, reported in ppb, were then totaled for each participant to give a single cumulative organochlorine pesticide residue value. The logarithm of these cumulative residue values was statistically analyzed using the matched-pairs analysis of variance procedures (Table 35). The mean residue value for the case cohort was 62.07 ppb, which was significantly higher than the corresponding mean value for the controls, 33.33 ppb. DDT and its metabolite, DDE, account for the large majority of these residues. As stated previously, 96% of the acute organophosphate exposures were occupationally related. Since a wide spectrum of pesticides, especially the OP and organochlorine insecticides, is commonly found in pesticide related occupations it is not surprising that the mean

Table 34. Relative's Assessment of Patient's Functioning: Test Score Means, Pooled Estimate of the Standard Error (S.E.) of Each Mean, and Probability Level of the Analysis of Variance Test for the Case-Control Comparison. Neuro-organophosphate Study, 1979.

Relative Rating: Personality	Means		S.E.	P-level*
	Cases	Controls		
Depression	2.04	1.66	.09	.005
Irritability	2.15	1.63	.11	.001
Seriousness	2.64	2.56	.10	-
Withdrawal	1.74	1.44	.11	.046
Careless in appearance	1.05	.88	.10	.150
Careless in activities	1.27	1.17	.11	-
Suspiciousness	1.66	1.45	.12	.229
Confusion about what is happening	1.03	.73	.10	.036
Confusion about what he/she is doing	.79	.67	.08	.301
Indifference	1.29	1.16	.09	.287
Unpredictable and changeable in attitudes	1.72	1.50	.10	.125
Unpredictable and changeable in behavior	1.78	1.44	.10	-
Inappropriate in social situations	1.24	1.23	.07	-
Selfish	1.26	1.36	.11	-
Upset by new problems	2.03	1.78	.13	.175
Upset by changes in plans	2.00	1.88	.13	-
Demanding of others' attention	1.87	1.87	.11	-**
Dependent upon others	1.34	1.26	.11	-
Dependability	1.20	1.04	.10	.280
Desirability as family member	1.06	.80	.11	.112

Relative Rating: Personality (Continued)	Means		S.E.	P-level*
	Cases	Controls		
Appreciation by others	.85	.84	.09	-
Confabulation	.77	.70	.12	-
Relative Rating: Memory				
For verbal communications in last day or two	1.54	1.45	.12	-
For verbal communications a year or more ago	1.46	1.51	.14	-
For events occurring in last day or two	.65	.58	.10	-
For events occuring a year or more ago	1.02	1.07	.11	-
For people met in last day or two	.42	.62	.10	.176
For people met a year or more ago	.96	1.13	.11	.248
Losing track of time	1.02	1.07	.13	-
Forgetting what he/she is doing	.51	.56	.10	-
Forgetting how to do things	.37	.28	.07	-
Losing things by forgetting where they are	1.58	1.68	.15	-
Forgetting obligations	1.30	1.29	.12	-
Relative Rating: Language and Communication				
Difficulties understanding speech of others	1.12	.78	.12	.049
Difficulties recognizing printed or written words	.79	.47	.11	.053
Difficulties understanding reading material	.68	.50	.10	.198
Difficulties with enunciation	.79	.66	.12	-
Difficulty thinking of names of things	1.10	.78	.10	.035
Other word finding difficulties	.92	.69	.09	.087

Relative Rating: Language and Communications (Cont'd)	Means		S.E.	P-level*
	Cases	Controls		
Difficulties forming letters correctly when writing	.60	.41	.09	.155
Others have difficulty reading his/her writing	.70	.66	.13	-
Difficulty spelling	1.52	1.39	.13	-
Relative Rating: Use of Hands				
Difficulty performing tasks with right hand	.38	.29	.10	-
Difficulty performing tasks with left hand	.43	.94	.12	.003
Relative Rating: Cognitive/Intellectual Functions				
Thoughts seem confused or illogical	.68	.40	.09	.028
Distracted from what doing or saying	.44	.55	.07	.297
Confusion about where patient is	.25	.20	.08	-
Difficulty finding way	.34	.24	.07	-
Difficulty calculating	.97	.86	.11	-
Difficulty planning and organizing activities	.85	.81	.09	-
Difficulty solving problems	.81	.70	.07	.274
Difficulty following directions	.52	.60	.08	-
Difficulty following instructions	.75	.67	.06	-

* The p-level is not given in cases for which the F-ratio is less than unity.

**The F-test for interaction between exposure groups and states is significant at the 5% level.

Table 35

Analysis of Variance Summary*
with Subgroup Means and Standard Deviations
for the Total Organochlorine Pesticide Residue in the Blood

Source of Variation	Degrees of Freedom	Mean Square	F-ratio	p-level
Between Pairs	85	.99		
States	1	13.30	15.77	<.001
Error A	84	.84		
Within Pairs	86	.91		
Exposure	1	10.13	12.63	<.001
State & Exp.	1	.74	<1	-----
Error B	84	.80		
Total, adj.	171	.95		

*The analysis of variance was performed on the logarithm of the cumulative organochlorine pesticide residue.

		Cases	Controls	Overall
Colorado Participants	Mean	33.46	22.94	28.20
	S.D.	24.20	13.01	20.00
Texas Participants	Mean	82.67	40.81	61.74
	S.D.	78.40	35.24	64.03
Overall	Mean	62.07	33.33	47.70
	S.D.	66.19	29.40	53.06

blood residue levels of the persistent organochlorine pesticides were significantly higher in the cases than in the controls.

The Texas participants in both the control and case cohorts had significantly higher residue values than the Colorado participants. This result might be expected since previous studies have shown that the body burden of organochlorine pesticide residues in residents of southern states is significantly greater than that of residents of northern states.

One of the purposes of testing the cases and controls for ChE depression was to determine if any of the participants showed evidence of exposure to OPs at the time of examination in as much as some of the controls as well as cases were in occupations where occupational or accidental exposure to OPs was possible.

Laboratory data on RBC and plasma ChE were statisitcally analyzed using the matched-pairs analysis of variance procedure; the results are presented in Tables 36 and 37, respectively. As seen in Tables 36 and 37, both the case and control cohorts were well above the lower limits of normal RBC ChE and plasma ChE. The approximate lower limits of normal for the pH STAT method are 8.0 μM/min/ml for RBC and 2.3 μM/min/ml for plasma. The mean values for plasma ChE for the control cohort was significantly lower than that for the case control.

Since the residue data showed a statistically significant difference between the case and control cohorts, this variable was analyzed to determine its potential influence on significant neurological findings. In particular, correlation coefficients were computed between the five most comprehensive neuropsychological measurements and the organochlorine residue level and the ChE levels. As previously mentioned, on four of these five neurospychological measurements, the control cohort preformed significantly better than the case cohort. The correlation analysis, failed to show any significant

Table 36

Analysis of Variance Summary
with Subgroup Means and Standard Deviations
for Red Blood Cell Cholinesterase

Source of Variation	Degrees of Freedom	Mean Square	F-ratio	p-level
Between Pairs	85	11.25		
States	1	442.38	72.31	<.001
Error A	84	6.12		
Within Pairs	86	6.21		
Exposure	1	1.99	<1	---
State & Exp.	1	1.26	<1	---
Error B	84	6.32		
Total, adj.	171	8.72		

		Cases	Controls	Overall
Colorado Participants	Mean	12.40	12.38	12.39
	S.D.	2.10	1.89	1.99
Texas Participants	Mean	15.82	15.46	15.64
	S.D.	2.96	2.61	2.79
Overall	Mean	14.39	14.17	14.28
	S.D.	3.13	2.78	2.95

Table 37

Analysis of Variance Summary
with Subgroup Means and Standard Deviations
for Plasma Cholinesterase

Source of Variation	Degrees of Freedom	Mean Square	F-ratio	p-level
Between Pairs	85	1.29		
States	1	.55	<1	----
Error A	84	.69		
Within Pairs	86	1.04		
Exposure	1	5.44	5.49	.021
State & Exp.	1	.68	<1	----
Error B	84	.99		
Total, adj.	171	1.17		

		Cases	Controls	Overall
Colorado Participants	Mean	4.90	4.70	4.80
	S.D.	1.16	.73	.96
Texas Participants	Mean	5.14	4.68	4.91
	S.D.	1.10	1.17	1.16
Overall	Mean	5.04	4.69	4.86
	S.D.	1.13	1.01	1.08

association between organochlorine residue and any of the summary neuropsychological variables. Thus, any assumptions of influence toward impaired neuropsychological function from exposure to organochlorine pesticides were not supported by these data. Similarly, the correlations of the ChE levels with the summary neuropsychological variables were not statistically significant. In fact, none of the correlation coefficients exceeded .25.

SUMMARY AND DISCUSSION

A basic hypothesis of this research was that individuals with previous documented acute organophosphate pesticide poisonings may experience latent chronic neurological effects. It should be emphasized that the study participants were not merely exposed to organophosphates, but they were made severely ill by the exposure to the organophosphate. The exposures were of such magnitude to require hospitalization in 78 per cent of the cases. It should also be emphasized that the mean number of days from post poisoning to neurological testing was 2574 days. This study was conducted by using matched-pairs to compare a cohort of 100 previous organophosphate poisoning cases to a cohort of 100 controls. The matching characteristics included age, sex, race, ethnic background, and social economic factors. All participants and controls came from the states of Colorado and Texas. In the blind study design, each study participant received a physical examination, neurological examination, electroencephalogram (EEG), and neuropsychological testing. Blood samples were collected from each participant for analyses for organochlorine pesticide residues and cholinesterase levels. In addition, the blood samples were evaluated for hematology, morphology, urea nitrogen and creatinine. All of the data obtained in this study were statistically analyzed using appropriate matched-pairs analyses.

The results of the physical examination revealed no significant differences between the case and control cohorts. Evaluations of the blind phases of this study revealed that the clinical EEG could not discriminate the case cohort from the matched control cohort. Previous investigators have indicated an association between EEG changes and exposure to organophosphate compounds. For example, Duffy et al.(13) reported on the brain electrical activity of workers exposed to sarin compared to that of control subjects; statistically significant group differences included increased beta activity, increased delta and theta slowing, decreased alpha activity and increased amounts of rapid eye movement during sleep in the exposed population. Duffy et al. concluded that their results, when considered with the long-term behavioral effects of OP exposure, "provided parallel evidence that OP exposure could produce long-term changes in brain function". The EEG data obtained in this study neither confirmed nor refuted these findings; whereas Duffy's results were based on quantitative data derived from the power spectral analysis of EEG's, the EEG data obtained in this study were clinically interpreted from visual readings by the electroencephalographer. (As mentioned previously, the computer breakdown at the University of Colorado Medical Center prevented the use of digitized spectral analyses of the EEG's).

However, this study found that some neurological deficiencies (e.g., mental status exam and peripheral sensory findings) occurred more frequently in the case participants. Although only a few of the differences between the two cohorts in the neurological examination were significant, several major differences between the case and control cohorts were found through the neuropsychological evaluations. Each of the five summary scores and each of the 34 subtest scores from the neuropsychological examination was analyzed using a matched-pairs analysis of variance procedure to determine the

statistical significance for the difference between the case and control cohorts. In summary of the neuropsychological results, it was found that the participants in the case cohort were significantly worse than the controls on four of five summary measures and on 18 of 34 individual subtest scores used in the study. The differences occurred on tests of widely varying abilities, including intellectual functioning, academic skills, abstraction and flexibility of thinking, and simple motor skills (speed and coordination). The case cohort did not perform significantly better than the control cohort on any of the subtests.

A total of 24% of the case cohorts obtained Halstead-Reitan Battery summary scores in the range that strongly suggested cerebral damage or dysfunction, whereas only 12% of the controls performed at the same level on these tests. Based on the matched-pairs chi-square test, this difference in proportions between the case and control cohorts was statistically significant ($p < .05$). It should be noted that the Halstead-Reitan Battery is the most comprehensive and best validated neuropsychological test battery currently available. In contains a number of tests, because it was designed to measure a wide range of adaptive abilities that can be affected by brain lesions involving various cerebral locations. Considering the complexity of the brain and the behaviors it subserves, the use of two or three tests of "organicity" in this study would have been inadequate. There are two summary measures from this battery that are more sensitive to brain lesions than are any of the individual tests (the Halstead Impairment Index and the Average Impairment Rating). The pesticide poisoned subjects did significantly worse than the controls on both of these measures. It should be noted that both cohorts showed above average intellectual functioning on the WAIS Battery.

The overall difference between the case cohort and the cohort of matched controls was further evaluated by analyzing simultaneously all 34 subtest scores in the neuropsychological evaluation. This analysis (a multivariate analysis of variance procedure for matched-pairs designs) found the total difference between the two cohorts to be highly significant ($p = .0076$). Furthermore, the lack of significance in the statistical test for "Interaction" in the multivariate analysis of variance confirmed that the difference between the case and control cohorts was consistent for the study cohort subgroups (i.e., Colorado and Texas). The subtests from each battery of neuropsychological tests (i.e., WAIS, Halstead-Reitan, Peabody, and Added Ability Tests) were also analyzed simultaneously using the same multivariate analysis of variance procedure. For each battery of tests, the difference between the case and control cohorts was statistically significant (the p-levels for the above four batteries were .0001, .0311, .0066, and .0055, respectively). For each battery, this difference between case and control cohorts was consistent for the two study subgroups from Colorado and Texas.

Results from the Patient Assessment of Own Functioning Inventory were similar to the findings of the objective neuropsychological testing. In the Patient Assessments, the difference between case and control cohorts was significant with respect to everyday functioning on 10 of 32 aspects of language and communication, memory, cognitive intellectual functions, and perceptual functions. The case participants also demonstrated significantly lower abilities in the same subject areas on objective testing as they did on the Patient Assessment Inventory.

Results from the inventory of Relative's Assessment of Patient Functioning showed fewer significant differences between the case and control cohorts than either the objective neuropsychological testing or the Patient Assessment of Own Functioning Inventory. The Relative's Assessment showed the case

cohort to have significantly more problems on four of 22 personality scale items: depression ($p = .005$); irritability ($p = .001$); confusion about what is happening ($p = .036$); withdrawal ($p = .046$). Based on the relative's assessment the case cohort was found to have significantly more difficulties in understanding speech of others ($p = .049$) and in thinking of names of things ($p = .035$).

MacMahon (51) has noted that, in the absence of experimental data, three types of considerations are useful in distinguishing between epidemiolgical associations that are causal and those that are secondary. These include time sequence, strength of association between two events, and consonance with existing knowledge.

Since the study was designed to investigate the chronic effects that might be associated with a previous acute organophosphate pesticide (OP) poisoning, the study purposely included those cases that had experienced severe OP intoxications. In particular, the study design for this research included only cases that had experienced an organophosphate poisoning of such severity to usually require hospitalization. The time lapse from the poisoning experiences to neurological examination ranged from 117 days for one case to 9640 days with the mean time lapse being 2574 days. To make certain that study participatants had not experienced recent OP exposures, blood samples were collected and anlayzed for cholinesterase depression.

With respect to the strength of association between acute organophosphate pesticide poisoning and neuropsychological deficits, one might reasonably expect the greater the dose the greater the neurological deficit --- this is, assuming the degree of neuropsychological deficits to be related to the dose (concentration, route of exposure, toxicity) at the time of the OP poisoning experience. Because of the lack of specific dose-type data, the study was

unable to relate degree of OP poisoning severity to the degree of neuropsychological deficit. However, the strength of the association between acute organophosphate exposure and neuropsychological deficits is reflected, not only in the number of statistically significant differences between the exposed and control cohorts, but more importantly in the consistency of these significant differences.

Obviously, in any epidemiologic study of this type, there is the potential for several confounding variables, including multiple exposures to low levels of OP compounds and other pesticides. In addition, there was a variation in the length of the latent induction period prior to the neuropsychological evaluations. There is also the question of the exact type of cerebral lesions in the exposed population. For example, does the pattern of deficits resemble diffuse arteriosclerosis, lead encephalopathy, or other diseases? It should be emphasized that there is some danger of overinterpreting patterns of group mean scores on neuropsychological test batteries, because this frequently implies more consistency than actually exists among the individual subjects in the group. Some research on use of the Minnesota Multiphasic Personality Inventory (MMPI) has been criticized on this basis. Also since no consistently focal or lateralized brain changes were expected in the poisoned group, the research design did not concentrate on looking for specific patterns of deficits among the cases. For example, although one might postulate that the case group data would include more involvement of the frontal areas than of the other cerebral areas this would probably be an overinterpretation of the results. The pattern of results on the WAIS battery, such as the greater group differences on Verbal than on Performance subtests, introduces the potential confounding variable of control selection. Although one might argue that an inadvertent bias in the selection of study controls could account

for the observed group differences on the WAIS, a selection bias of this nature would not account for the greater number of poisoned subjects scoring in the brain damaged range on the Halstead-Reitan Battery.

It might be argued that residual effects from cerebral anoxia due to organophosphate poisoning may cause the observed neuropsychological differences. However, selection criteria were designed to eliminate both cases and controls who were known to be unconscious for a significant period of time (more than 15 minutes) in his or her lifetime, regardless of the cause. In addition, the selection criteria eliminated any subjects whose medical history included any disease that might adversely influence the neurological and neuropsychological testing. In particular, the subject screening procedures excluded any subjects who had a past history of neurological illness, signficant head trauma, or substance abuse.

The neurological and neuropsychological evaluations are obviously complementary in that each emphasizes different aspects of dysfunction. The clinical neurological examinations focus primarily on sensory and motor functioning with very little attention to the higher level cognitive and intellectual functions that are very sensitively assessed by the neuropsychological procedures. Both examinations found no differences between the case and control cohort participants with respect to sensory-perceptual functioning. The neuropsychological exam found some mild impairment of fine coordination and motor speed with the upper extremities in the case cohort. The major neuropsychological differences between case and control cohorts appeared on tests of abilities that receive limited evaluation in the clinical neurological examination. The two methods of evaluation, taken together, thus provide a more complete evaluation of brain function not possible utilizing either examination alone. Hopefully future research will

help to further elucidate the important interrelationships (person-place-time chemical) between acute organophosphate exposure and chronic neuropsychological health effects.

REFERENCES

1. Expert Committee on Insecticides. Safe Use of Pesticides. 20th Report, WHO Tech. Rep. Ser. No. 513, World Health Organization, 1973. p. 42.

2. Colorado Epidemiologic Pesticide Studies Center. A Study of Hospitalized Acute Pesticide Poisonings in the United States, 1971-1973. Colorado State University, Fort Collins, Colorado, 1975. p. 32.

3. Durham, W.F. and W.J. Hayes, Jr. Organic Phosphorus Poisoning and Its Therapy. Arch. Environ. Health 5:21-53, 1962.

4. Murphy, S.D. Pesticides. In: Toxicology - The Basic Science of Poisons, L. J. Casarett and J. Doull, eds. MacMillian Publishing Co., Inc., New York, 1975. p. 424.

5. Hunter, D. The Diseases of Occupations. English University Press, London, England, 1975. pp. 368-377.

6. Bidstrup, P.L., J.A. Bonnell, and A.G. Beckett. Paralysis Following Poisoning by a New Organic Phosphorus Insecticide (Mipafox). Brit. Med. J. 1:1063-1072, 1953.

7. Gershon, S. and F.H. Shaw. Psychiatric Sequelae of Chronic Exposure to Organophosphorus Insecticides. Lancet 1:1371-1374, 1961.

8. Dille, J.R. and P.W. Smith. Central Nervous System Effects of Chronic Exposure to Organophosphate Insecticides. Aerosp. Med. 35:475-475, 1964.

9. Drenth, H.J. Neuromuscular Function in Agricultural Workers Using Pesticides. Arch. Environ. Health 25:395-398, 1972.

10. Grob, D. and A.M. Harvey. The Effects and Treatment of Nerve Gas Poisoning. Amer. J. Med. 14:52-63, 1953.

11. Brown, H.W. Electroencephalographic Changes and Disturbance of Brain Function Following Human Organophosphate Exposure. Northwest Med. 70: 845-846, 1971.

12. Metcalf, D.R. and J.H. Holmes. EEG, Psychological and Neurological Alterations in Humans with Organophosphorus Exposure. Ann. N.Y. Acad. Sci. 160:357-365, 1969.

13. Duffy, F.H., J.L. Burchfiel, P.H. Bartels, M. Gaon, and V.M. Sim. Long-Term Effects of an Organophosphate upon the Human Electoencephalogram. Toxicol. Appl. Pharmacol. 47:161-176, 1979.

14. Barnes, J.M. (Letter). Lancet 2:102-103, 1961.

15. Bidstrup, P.L. (Letter). Lancet 2:103, 1961.

16. Stroller, A., J. Krupinski, A.J. Christophers, and A.K. Blanks. Organophosphorus Insecticide and Major Mental Illness. Lancet 1:1387-1388, 1965.

17. Tabershaw, I.R. and W.C. Cooper. Sequelae of Acute Organic Phosphate Poisoning. J. Occ. Med. 8:5-10, 1966.

18. Clark, G. Organophosphate Insecticides and Behavior, a Review. Aerospace Med. 42:735-740, 1971.

19. Holmes, J.H., Clinical Studies of Exposure to the Organophosphorus Insecticides. In: Research in Pesticides. C.O. Chichester, ed. Academic Press, New York, 1965. p. 315-327.

20. Savage, E.P., Bagby, J.R., Jr., Mounce, L.M., Williams, L.P., Jr., Cholas, G.: Pesticide Poisonings in Rural Colorado. Rocky Mt. Medical Journal, April 1971.

21. Gallaher, G.L. "Low Volume" Insect Control and Parathion Poisoning. Texas Med. 63:39, 1967.

22. Hatcher, R.L. and J.S. Wiseman. Epidemiology of Pesticide Poisoning in the Lower Rio Grande Valley in 1968. Texas Med. 65:40-43, 1969.

23. Hollingshead, A.B. The Two Factor Index of Social Position. Mimeo, Yale University, New Haven.

24. Wechsler, D. Manual for the Wechsler Adult Intelligence Scale. The Psychological Corporation, New York, 1955.

25. Halstead, W.C. Brain and Intelligence: A Quantitative Study of the Frontal Lobes. University of Chicago Press, Chicago, 1947.

26. A Research Program on the Psychological Effects of Brain Lesions in Human Beings. In: International Review of Research in Mental Retardation, N.R. Ellis, ed. Academic Press, New York, 1966.

27. Reitan, R.M. and L.A. Davidson (ed.). Clinical Neuropsychology: Current Status and Applications. Wiley & Sons, New York, 1974.

28. Russell, E.W., C. Neuringer, and G. Goldstein. Assessment of Brain Damage: A Neuropsychological Key Approach. Wiley-Interscience, New York, 1970.

29. Matarazzo, J.D. Wechsler's Measurement and Appraisal of Adult Intelligence. Williams & Wilkins, Baltimore, 1972.

30. Heaton, R.K. (Private Publication) Manual for Administration of Neuropsychological Test Batteries for Adults and Children. Indianapolis, 1969.

31. Saetveit, J.G., D. Lewis, and C.E. Seashore. Revision of the Seashore Measure of Musical Talents. University of Iowa Press, Iowa City, 1940.

32. Armitage, S.G. An Analysis of Certain Psychological Tests Used for the Evaluation of Brain Injury. Psychol. Monogr. 60:1, 1946.

33. Wheeler, L. and R.M. Reitan. The Presence and Laterality of Brain Damage Predicted from Responses to a Short Sphasia Screening Test. Percept. Mot. Skills 15:783, 1962.

34. Halstead, W.C. and J.M. Wepman. The Halstead-Wepman Aphasia Screening Test. J. Speech Hearing Dis. 14:9, 1949.

35. Dunn, L.M. and S.C. Markwardt, Jr. Peabody Individual Achievement Test Manual. American Guidances Service, Circle Pines, Minnesota, 1970.

36. Thurstone, L.L. Primary Mental Abilities. University of Chicago Press, Chicago, Ill., 1938.

37. Reitan, R.M. Verbal Problem Solving as Related to Cerebral Damage. Percept. Mot. Skills 34:515-524, 1972.

38. Berg, E.A. A Simple Objective Technique for Measuring Flexibility in Thinking. J. Gen. Psychol. 39:15-22, 1948.

39. Grant, D.A. and E.A. Berg. A Behavioral Analysis of Degree of Reinforcement and Ease of Shifting to New Responses in a Weigl-Type Card-Sorting Problem. J. Exp. Psychol. 38:404-411, 1948.

40. Reitan, R.M. Unpublished Test Modified by R.K. Heaton. University of Colorado Medical Center, Denver, Colorado.

41. Hathaway, S.R. and J.C. McKinley. The MMPI Manual. The Psychological Corporation, New York, 1951.

42. Dahlström, W.G., G.S. Welsch, and L.E. Dahlström. An MMPI Handbook, Vol. 1: Clinical Interpretation. University of Minnesota Press, Minneapolis, 1972.

43. An MMPI Handbook, Vol. II: Research Application. University of Minnesota Press, Minneapolis, 1975.

44. Winer, B.J. Statistical Principles in Experimental Design. McGraw Hill Book Company, New York, 1962. pp. 191-195.

45. Fleiss, J.L. Statistical Methods for Rates and Proportions. John Wiley & Sons, New York, 1973. pp. 72-80.

46. Stuart, A. A Test for Homogeneity of the Marginal Distribution in a Two-Way Classification. Biometrika 42:412-416, 1955.

47. Morrison, D.F. Multivariate Statistical Methods. McGraw-Hill Book Co., New York, 1967.

48. Milner, B. Some Effects of Frontal Lobectomy in Man. In: Frontal Granular Cortex and Behavior, J.M. Warren and K. Akert, eds. McGraw-Hill, New York, 1964.

49. Drewe, E.A. The Effect of Type and Area of Brain Lesion on Wisconsin Card Sorting Test Performance. Cortex 10:159-170, 1974.

50. Wechsler, D.E. A Standardized Memory Scale for Clinical Use. J. Psychol. 19:89-95, 1945.

51. MacMahon, B. and Thomas, F.P. Epidemiology Principles and Methods. Little, Brown and Company, Boston, 1970.